Severe Humoral Hypercalcemia in Primary Isolated Non-Hodgkin's Lymphoma of the Heart

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The etiology of hypercalcemia was investigated in a patient with primary isolated non-Hodgkin's lymphoma of the heart. There was no evidence of bone involvement, and parathyroid hormone and calciterol levels were suppressed. Plasma parathyroid-hormone–related protein (PTHrP 1-86) detected by immunoradiometric assay was increased (15 pmol/l compared with < 0.3 pmol/l in a control). We demonstrated that PTHrP was the humoral mediator of severe hypercalcemia in our patient. **Med. Pediatr. Oncol. 28:183–186** © 1997 Wiley-Liss, Inc.

Key words: hypercalcemia; non-Hodgkin's lymphoma; cardiac neoplasm; parathyroid-hormone–related protein

INTRODUCTION

Involvement of the heart in lymphoma is common in disseminated disease. Primary isolated cardiac lymphoma, defined as involving only the heart and pericardium, is extremely rare with a non-Hodgkin's lymphoma predominance [1]. In most reported cases of cardiac lymphoma, the clinical manifestations were life-threatening cardiac complications rather than typical lymphoma symptoms [1]. Although cardiac lymphoma cannot be clinically differentiated from other tumors of the heart, patients with lymphoma have a better prognosis [2].

Hypercalcemia is a serious and not infrequent complication of lymphoma and other malignant diseases that increases their morbidity and mortality [3]. The causes of malignancy-related hypercalcemia include local osteolysis, calciterol hyperactivity (which is the most frequent cause of hypercalcamia seen in lymphoma patients), and secretion of humoral mediators [4–9].

We describe a patient with primary isolated non-Hodgkin's lymphoma of the heart and severe hypercalcemia. The etiology of the hypercalcemia was found to be increased parathyroid-hormone–related protein (PTHrP) activity due to uncontrolled production of this protein by tumor cells. To the best of our knowledge, a similar association has not been described before.

CASE REPORT

A 60-year-old man presented with exertional dyspnea, weakness, and chest discomfort of 1 month's duration. There was no history of night sweats, fever, or pruritus. Physical examination demonstrated diminished breath sounds in the lung bases. There were neither signs of right heart failure nor enlarged lymph nodes, and the rest of the physical examination was normal.

Hematology and chemistry tests including calcium levels were normal. Radiographs and computed tomography (CT) of the chest showed an enlarged heart silhouette and bilateral pleural effusions. Transthoracic echocardiographic study demonstrated a pericardial effusion. Cytologic examinations of aspirated pericardial fluid showed undefined malignant cells, but the pleural fluid was negative for malignancy.

A primary site was not identified despite an extensive work-up. Pericardiocentesis was performed with complete resolution of the symptoms as well as the pericardial and pleural fluid resolved. During the next 6 months, the patient was asymptomatic. CT of the chest, abdomen, and pelvis were normal, as were cancer markers.

Severe weakness and edema of the legs developed 6 months later, and right heart failure was found. A technically difficult transthoracic echocardiographic study demonstrated a thickened pericardium, with normal left and right ventricular systolic function. Because the right heart failure persisted after pericardiocentesis, constrictive pericarditis was suspected. A right heart catheterization was then performed, but the catheter could not be advanced into the right atrium. Contrast injection into the superior vena cava showed a huge mass occupying and obstructing the right atrium and right ventricular inflow. Transesophageal echocardiographic study clearly visualized a large echogenic mass occupying the right atrium

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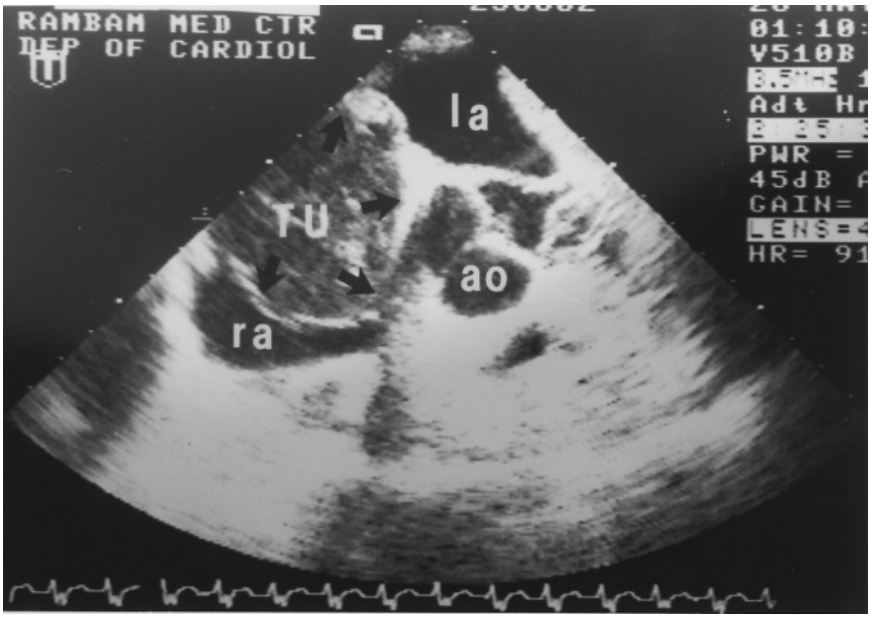

Fig. 1. A transesophageal echocardiographic study demonstrating a large echogenic mass occupying the right atrium and penetrating into the right atrial wall. TU = tumor; la = left atrium; ao = aorta; ra = right atrium.

and penetrating into the right atrial wall (Fig. 1). Emergency surgery was performed, and a large mass infiltrating the right atrial wall and obstructing the right atrial lumen was found. Partial resection of the mass led to restoration of the blood flow from the inferior and superior vena cava.

The surgical specimen consisted of a few fragments of soft, white material mixed with fatty, yellow tissue containing a few hemorrhagic areas. Histologic examination revealed dense infiltration of the myocardium and endocardium by a diffuse tumor with necrotic foci (Fig. 2). Immunoperoxidase stains were strongly positive in many cells for CD20 and 4KB5 (B-cell markers) and focally to immunoglobulin (Ig)M. T-cell markers (UCHL1 and A6) were negative in the tumor cells, as were stains for epithelial cells. All the above findings were consistent with malignant lymphoma, diffuse large cell-B type.

Hypercalcemia of 3.7 mmol/1 (normal, 2.12–2.69 mmol/l) had been found when right heart failure first appeared. This was before corticosteroids or cytotoxic drugs were administered. Inorganic phosphate at the time was 0.72 mmol/1 (normal, 0.9–1.6 mmol/l), albumin was 40 g/l (normal 35–55 g/l), and creatinine was 104 mmol/l (normal, 35–115 mmol/l). Intact parathyroid hormone (PTH) 1-84 was 0.25 pmol/l (normal, 1–5.7 pmol/l), calcitonin was 92 ng/1 (normal 42–88 ng/l), 25-hydroxyvitamin D was 6.2 μg/l (normal 20–50 μg/l), and 1, 25, hydroxyvitamin D was 16 pg/1 (normal 20–50 pg/l).

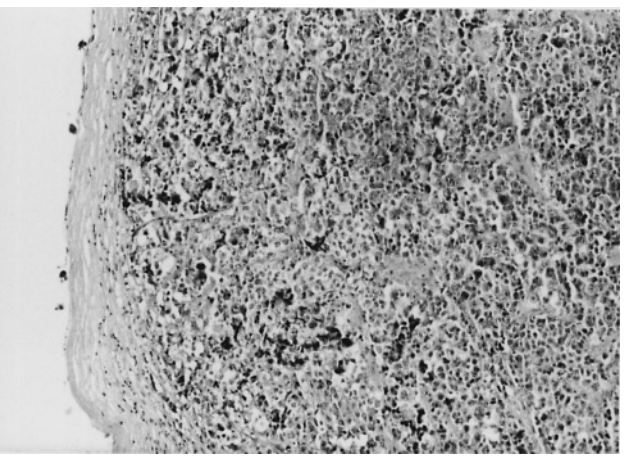

Fig. 2. Histologic examination of resected right atrial tumor showing the endocardium on the left. The myocardium is infiltrated by a diffuse tumor of the malignant lymphoma, diffuse large cell-B type. Hematoxylin-eosin, original magnification ×100.

PTHrP 1-86 detected by a two-site immunoradiometric assay was markedly increased to 15 pmol/l compared with less than 0.3 pmol/l in normocalcemic controls.

Lymphoma was restricted to the heart; there was no clinical radiographic or scintigraphic evidence of other organ involvement. Bone marrow aspiration and bone

biopsy were normal. A gallium scan showed pathologic uptake only in the heart.

During the following months, the patient had six courses of cytoxan, doxorubicin, vincristine, and prednisone (CHOP) with complete regression of heart failure and hypercalcemia. Four months after surgery, however, right heart failure and hypercalcemia of 3.5 mmol/l with elevated PTHrP levels were again found. A transesophageal echocardiographic study demonstrated a large posterior extracardiac mass compressing the right atrium, with superior and inferior vena caval dilatation. Another chemotherapy regimen (dexacort, vincristine, ifosfamide, and cisplatin [DVIP] and radiotherapy were instituted, but without response. The patient died of intractable heart failure 20 months after presentation.

DISCUSSION

The diagnosis of primary isolated non-Hodgkin's lymphoma, B cell of the heart was based on histologic examination of the resected right atrial tumor.

Primary cardiac tumors are extremely rare, with less than 1% of them being lymphomas [1]. Clinical manifestations include life-threatening complications such as pericardial effusion, tamponade, arrhythmias, superior vena cava syndrome, heart failure, and fatal pulmonary embolism. Lymphoma of the heart has frequently been diagnosed only at postmortem examination [1].

The main clinical features of the right atrial tumor at presentation in our patient were primary symptoms of heart disease; neither systemic manifestations of lymphoma nor lymphadenopathy or signs of other organ involvement were present. Cytologic examination of the aspirated pericardial effusion showed only undefined malignant cells, demonstrating again the limited role of cytology in assessing lymphomas [10]. Six months later, right heart failure and severe hypercalcemia developed. Right heart catheterization, transesophageal echocardiography, and emergency surgery with tumor resection led to the correct diagnosis. Appropriate chemotherapy could then be instituted, which resulted in regression of both heart failure and hypercalcemia. The relatively favorable prognosis of lymphoma compared with other primary malignant cardiac tumors was demonstrated by our patient surviving 20 months after presentation.

Hypercalcemia is a known complication of various malignant diseases and is most often related to bone metastases. In their absence, other mechanisms must be involved [5–9]. Seymour et al. [7] studied 22 patients with non-Hodgkin's lymphoma and hypercalcemia and found B-cell disease, similar to that seen in our patient, in 20. These investigators found calciterol levels in non-Hodgkin's lymphoma patients with hypercalcemia to be elevated when compared with a control group of patients with hypercalcemia without lymphoma.

Although 15% of patients with non-Hodgkin's lymphoma develop hypercalcemia at some stage during their disease [4], the extreme hypercalcemia found in our patient is unusual [6]. Lack of evidence for bone involvement indicated a humoral mechanism, and the suppressed PTH and calciterol levels were consistent with increased PTHrP activity. This was demonstrated in the plasma using a immunoradiometric assay.

PTHrP has been proposed as a contributing factor, rather than the major factor, for hypercalcemia in patients with lymphoma [7]. Seymour et al. [7] found increased PTHrP activity in only 2 of 22 patients with non-Hodgkin's lymphoma and hypercalcemia, both with increased calciterol activity. In some patients with lymphoma and hypercalcemia, neither bone involvement nor increased calciterol or PTHrP activity was found, indicating that other mediators might be involved [11].

There are several case reports regarding primary lymphoma of the liver and the kidney associated with humoral hypercalcemia [12,13]. To the best of our knowledge, there is only one other report of a patient with disseminated non-Hodgkin's B cell lymphoma in which increased PTHrP activity was found to be the only mediator for hypercalcemia [9]. Nonetheless, our patient is unique in that his lymphoma involved the heart.

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